Photoreceptor Rosettes in Autosomal Dominant Retinitis Pigmentosa With Reduced Penetration

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We performed histopathologic and immunofluorescence studies of autopsy eyes from a 73-year-old woman with autosomal dominant retinitis pigmentosa from a family with reduced penetrance. Light microscopic examination showed extensive photoreceptor loss in most regions. In the temporal midperiphery of the retina, there were patches of remaining photoreceptors, some arranged in rosettes. Electron microscopic examination showed that these rosettes were composed mostly of rods, with a few cone-like inner segments. The malformed photoreceptor elements in the rosette lumens stained positively with anti-rhodopsin, but not with anti-red- and green-cone opsin or anti-blue-cone opsin. To our knowledge, this is the first report of photoreceptor rosettes containing rod photoreceptors in a case of retinitis pigmentosa. Future studies of additional patients will be needed to determine if the rod-abundant rosettes seen in our patient are a characteristic finding of autosomal dominant retinitis pigmentosa with reduced penetrance.

A previously reported study of autopsy eyes from a young adult man with autosomal dominant retinitis pigmentosa in a family with reduced penetrance showed some degeneration of rods and cones with a relatively well-preserved retinal pigment epithelium and inner retina. We evaluated the autopsy eyes from a 73-year-old woman with autosomal dominant retinitis pigmentosa from a family with reduced penetrance to further define the histopathologic changes in this condition.

Our patient was a member of a family (No. 6778) in which retinitis pigmentosa (RP) was most likely inherited by a dominant mode with reduced penetrance (Figure 1). She was examined by us at age 62 years; at that time her visual acuity was hand motions in both eyes. Her son and daughter-in-law were unaffected but her grandson was affected. Full-field electroretinograms from these 4 family members are shown in Figure 2. The fundus examination findings of retinal-arteriolar attenuation and bone-spicule pigmentation around the midperiphery of the eye confirmed the diagnosis of RP in the donor and her grandson. The absence of electroretinogram abnormalities in the daughter-in-law helped to exclude an X-linked mode of transmission in this family.

The patient died of a cerebrovascular accident at the age of 73 years. Her eyes were fixed 40 minutes after death. The right eye was fixed in 2.5% glutaraldehyde and 1% formaldehyde in 0.1-mol/L phosphate buffer solution and was examined by light microscopy and electron microscopy. The left eye was fixed in 4% formaldehyde in 0.1-mol/L phosphate buffer solution. Cryosections were used for immunofluorescence studies using 3 antibodies: a polyclonal antibody that reacts with blue-cone opsin, provided as shown by Lerea et al, a polyclonal antibody that reacts with red- or green-cone opsin, and a monoclonal antibody named 1D4 that reacts with rhodopsin, provided by Molday. Controls were autopsy eyes from an 80-year-old unaffected woman.
PATHOLOGIC FINDINGS

Gross examination revealed unremarkable anterior segments; the posterior segments showed intraretinal bone-spicule pigmentation 360° around the midperiphery and far periphery of the retina, a diffusely tiroid appearance with prominent chorioidal vessels (especially in the posterior pole), pale optic discs, attenuated retinal vasculature, and atrophy of the retinal pigment epithelium and choroid throughout the macula. Light microscopy showed extensive photoreceptor degeneration. In the temporal midperiphery, some photoreceptors could be seen in small patches. In addition, some photoreceptor cells formed radial arrangements around empty lumens, thus forming rosettes (Figure 3, A). Part of the wall of each rosette was formed by the retinal pigment epithelium. Electron microscopy showed that the photoreceptors in the walls of the rosettes were mostly rods, with a few residual conelike inner segments (Figure 3, B). Immunofluorescence studies with anti-rhodopsin antibody confirmed that most of the remaining photoreceptors were rods (Figure 3, C). No photoreceptor cells reacted with antibodies against red- and green-cone opsin, or blue-cone opsin (Figure 3, D and E). The light microscopy, electron microscopy, and immunofluorescence studies from an 80-year-old unaffected control are shown for comparison (Figure 4).

COMMENT

Photoreceptor rosettes, each with a row of photoreceptors arranged radially around a central lumen, have been previously described in only 2 cases of RP; both patients were of unknown genetic type. The first patient was a 76-year-old man who had rosettes composed mostly of blue cones. The second patient was a 56-year-old man with clumped...
Figure 3. Micrographic views of our patient’s eyes: A, Light micrographic view shows areas of remaining photoreceptors in the temporal midperiphery of the retina as well as rosettes (arrows) (bar=60 µm); B, Electron micrographic view shows rod photoreceptors, with a few conelike inner segments found in a partial rosette (bar=8 µm). C, Immunofluorescence study. Left, The photoreceptor cells forming a rosette react to anti-rhodopsin antibody. Right, The same section viewed with Nomarski optics. D, Immunofluorescence study. Left, The same region as in C shows a lack of immunoreactivity to anti–red- and green-cone opsin antibody. Right, The same section viewed with Nomarski optics. E, Immunofluorescence study. Left, The same region as in C shows a lack of immunoreactivity to anti–blue-cone opsin antibody. Right, The same section viewed with Nomarski optics (bar[C−E]=20 µm) (R indicates rod; C, cone; OS, outer segment; RPE, retinal pigment epithelium; and M, macrophage).

Figure 4. Micrographic views of an 80-year-old unaffected female control: A, Light micrographic view of the temporal midperiphery of the retina (bar=40 µm). B, Electron micrograph (bar=8 µm). C, Immunofluorescence study. Left, The temporal midperiphery of the retina shows immunoreactivity to anti–rhodopsin antibody. Right, The same section viewed with Nomarski optics. D, Immunofluorescence study. Left, The same region as in C shows immunoreactivity to anti–red- and green-cone opsin antibody. Right, The same section viewed with Nomarski optics. E, Immunofluorescence study. Left, The same region as in C shows immunoreactivity to anti–blue-cone opsin antibody. Right, The same section as viewed with Nomarski optics [bar[C−E]=20 µm] (GC indicates ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; IS, inner segments; OS, outer segments; RPE, retinal pigment epithelium; CH, choroid; C, cone; and R, rod).
pigmentary retinal degeneration, a variant of RP.\(^6\) The types of photoreceptors in the rosettes of this second case were not identified.

Our patient represents the third example of photoreceptor rosettes in RP. To our knowledge, this is the first case of RP with photoreceptor rosettes containing rods. The inheritance pattern seems to be dominant with reduced penetrance. This pattern is usually due to a mutation in an unidentified gene, called \(RP11\), on chromosome 19q.\(^7\) We could not determine if our patient had RP due to the \(RP11\) gene because we could not successfully retrieve DNA from the fixed ocular tissues, and the small number of living family members prevented statistically significant DNA-linkage analysis. The pronounced delay in the cone electroretinogram implicit time (cone b-wave implicit time, 48 milliseconds; normal, \(\leq 32\) milliseconds) found in the patient’s 15-year-old affected grandson supports the categorization of this family’s disease as being due to the \(RP11\) gene, since implicit times prolonged to approximately 50 milliseconds have been observed in other families with \(RP11\)-linked disease.\(^7\) Precise genetic categorization of our patient must await future DNA analysis once the \(RP11\) gene is identified.

It is unknown if rosettes in RP are specific to a particular gene. The photoreceptors composing the rosettes can differ, since they were blue cones in a previous case and rods in our case. Since 1 of the previously described cases had clumped pigmentary degeneration rather than typical RP, it is likely that different genetically defined forms of RP can exhibit rosettes. The pathogenic mechanism leading to the formation of rosettes remains unknown.

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REFERENCES


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